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B23

Japanese Patent Application No. 75427/1983
Date of Application: April 28, 1983
Japanese Patent Public Disclosure No. 204175/1984
Date of Disclosure: November 19, 1984
Inventors: T. Wakabayashi and two others
Applicant: TERUMO CORP.

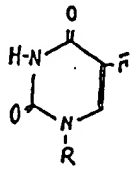
SPECIFICATION

1. Title of Invention

5-Fluorouracil derivatives, platelet aggregation inhibitors using said derivatives, and cancer metastasis preventives using said derivatives

2. Claims

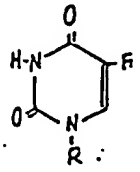
(1) A 5-fluorouracil derivative represented by the general formula:



(where R is an acyl group derived from a hexaenoic higher aliphatic acid).

(2) A 5-fluorouracil derivative according to claim 1, wherein R is an acyl group derived from 4,7,10,13,16,19-docosahexaenoic acid.

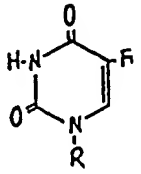
(3) A platelet aggregation inhibitor using a 5-fluorouracil derivative represented by the general formula:



(where R is an acyl group derived from a hexaenoic higher aliphatic acid)

(4) A platelet aggregation inhibitor using a 5-fluoro-uracil derivative according of claim 3, wherein R is an acyl group derived fro 4,7,10,13,16,19-docosahexaenoic acid.

(5) A cancer metastasis preventive using a 5-fluoro-uracil derivative represented by the general formula:



(where R is an acyl group derived from a hexaenoic higher aliphatic acid).

(6) A cancer metastasis preventive using a 5-fluoro-uracil derivative according to claim 5, wherein R is an acyl group derived from 4,7,10,13,16,19-docosahexaenoic acid.

3. Detailed Description of Invention

I. Background of the Invention

Technical Field

The present invention relates to 5-fluorouracil derivatives, platelet aggregation inhibitors using said derivatives, as well as cancer metastasis preventives using said derivatives.

The 5-fluorouracil derivatives provided by the present invention are novel compounds and having a potent platelet aggregation inhibiting action, they are useful as cancer metastasis preventives. They are also useful as cancer control agents.

Prior Art

5-Fluorouracil is known to have a salient cancer control action. As for 4,7,10,13,16,19-docosahexaenoic acid, it has been reported that this compound is abundant in fish oils.

The present inventors synthesized hexaenoic higher aliphatic acid amides of 5-fluorouracil and intensively studied their pharmacological activities. As a result, it has been found that the amides have a salient platelet aggregation inhibiting action and a cancer metastasis inhibiting action.

II. Objects of the Invention

An object of the present invention is to provide novel 5-fluorouracil derivatives useful as platelet aggregation inhibitors and cancer metastasis preventives.

Another object of the present invention is to provide

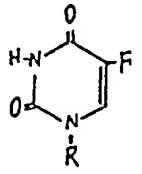
5-fluorouracil derivatives that are particularly useful as cancer metastasis preventives.

Yet another object of the present invention is to provide 5-fluorouracil derivatives useful as cancer control agents.

III. Specific Description of the Invention

There objects of the present invention can be attained by the techniques set forth below.

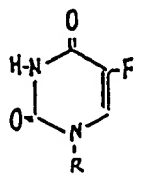
Thus, the present invention relates to a 5-fluorouracil derivative represented by the general formula:



(where R is an acyl group derived from a hexaenoic higher aliphatic acid).

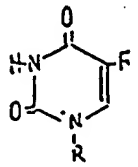
In the general formula set forth above, R is desirably an acyl group derived from 4,7,10,13,16,19-docosahexaenoic acid.

The present invention also relates to a platelet aggregation inhibitor using a 5-fluorouracil derivative represented by the general formula:



(wherein R is an acyl group derived from a hexaenoic higher aliphatic acid).

Further, the present invention relates to a cancer metastasis preventive using a 5-fluorouracil derivative represented by the general formula:



(where R is an acyl group derived from a hexaenoic higher aliphatic acid).

In the general formula for the 5-fluorouracil derivatives which are provided by the present invention, R represents an acyl group derived from a hexaenoic higher aliphatic acid and it signifies a group that is left by removing a hydroxyl group from a higher aliphatic acid having six cis-form double bonds in the carbon chain. Preferred examples of the higher aliphatic acid are those having 22 - 24 carbon atoms.

The compound which is the most preferred as the 5-fluorouracil derivative represented by the general formula set forth above is 1-(4,7,10,13,16,19-docosahexenoyl)-5-fluorouracil.

The compound represented by the general formula set forth above can be produced by reacting a hexaenoic higher

aliphatic acid with 5-fluorouracil in the presence of a condensing agent or by reacting a reactive derivative of a hexaenoic higher aliphatic acid with 5-fluorouracil. Examples of the condensing agent include 2-chloro-1-methylpyridinium p-toluenesulfonate and 2-bromo-1-methylpyridinium iodide. Exemplary reactive derivatives of a hexaenoic higher aliphatic acid include acid anhydrides and esters of N-hydroxysuccinimide.

The 5-fluorouracil derivatives of the present invention are characterized by having a platelet aggregation inhibiting action. The 5-fluorouracil by having a platelet aggregation inhibiting action. The 5-fluorouracil derivatives of the present invention can be used as cancer metastasis preventives or cancer control agents; the dose varies with the severity of the disease and the daily dose ranges from about 0.1 to about 5 g per adult and, depending on the need, the administration may be done once, twice or three times a day. The route of administration may be peroral or by intravenous or subcutaneous injection.

The compounds of the present invention are mixed with pharmaceutical carriers or excipients by conventional methods such that they are formulated as tablets, powders, capsules or granules. Exemplary carriers or excipients include calcium phosphate, corn starch, potato starch, sugar, lactose, talc, magnesium stearate and gum arabic. Coatings may be applied to tablets in accordance with the usual method. Besides the solid dosage forms described

above, the compounds of the present invention may be formulated as liquids, for example, oil-base suspensions and syrups.

The compounds of the present invention have six double bonds in the molecule, so they permit the incorporation of α-tocopherol, α-tocotrienol, etc. as stabilizers. Alternatively, the compounds of the present invention may be stabilized by encapsulation with cyclodextrin.

The present invention will now be described more specifically by reference to a working example and test cases.

Examples

4,7,10,13,16,19-Docosahexaenoic acid (361 mg) was dissolved in anhydrous 1,2-dichloroethane (5 ml) in an argon stream; to the solution, 2-chloro-1-methylpyridinium p-toluenesulfonate (363 mg), 5-fluorouracil (143 mg) and triethylamine (245 mg) were added sequentially, and the resulting mixture was stirred at room temperature for 24 h. After concentration the reaction solution, n-pentane (10 ml) and water (5 ml) were added and the mixture was stirred. Subsequently, the pH of the stirred mixture was adjusted to about 4 with 0.5 N oxalic acid, followed by extraction with n-pentane. The n-pentane layer was washed with saturated brine and dried with Glauber's salt. The extract was evaporated to dryness under vacuum and the residue was subjected to column chromatography using Sephadex LH-20 (30 g) and

1-(4,7,10,13,16,19-docosahexenoyl)-5-fluorouracil (287 mg, 59%) was obtained from the methylene chloride eluted fraction. This compound had the following physicochemical data:

IR($CHCl_3$) ν_{max} cm^{-1} : 1725, 1680, 1325, 1260

NMR($CDCl_3$) δ (ppm) : 0.97(3H,t,J=7.4Hz), 3.20(2H,t,J=7.1Hz), 5.38(12H,m,olefinic proton)

Test Cases

Platelet aggregation inhibiting action

Nine volumes of blood were withdrawing from a rabbit carotid artery using a syringe filled with a 3.8% sodium citrate solution (one volume). The blood sample was centrifuged to separate platelet rich plasma (PRP with 5 x 10^6 platelets per μ L). A portion (250 μ L) of the PRP was put into a cuvette and heated in a thermostatic chamber (37℃) for 2 min; thereafter, 20 μ L of 1-(4,7,10,13,16, 19-docosahexanoyl)-5-fluorouracil in solution (1.4 x 10^{-2} M ethanol solution diluted with a 1:3 mixture of Tris-buffered isotonic aqueous solution of sodium chloride and physiological saline) was added and the resulting mixture was incubated for 30 min; thereafter, 10 μ L of arachidonic acid (100 μ M) was added as an aggregation inducer and the aggregation of platelets was measured. The platelet aggregation induced by arachidonic acid could be 50% inhibited by 1-(4,7,10,13,16,19-docosahexanoyl)-5-fluorouracil at a

concentration of 9×10^{-5} M.

Cancer metastasis preventing effect

Lewis lung cancer cells (10^6) were diluted in physiological saline and inoculated under the skin of BDF_1 mice 5 weeks old after birth. Each of the control and test groups consisted of 6-8 mice. After 24 h of the transplantation, the mice were administered a 0.5% CMC suspension of 1-(4,7,10,13,16,19-docosahexanoyl)-5-fluorouracil (100 mg/kg) perorally for 5 consecutive days. The efficacy of the test compound was evaluated in terms of percent index of life survival relative to the control group. The result was 64% survival.

$$\text{Percent index of life survival (ILS\%)} = \frac{\text{Mean number of days of survival of the group treated} - \text{Mean number of days of survival of the control group}}{\text{Mean number of days of survival of the control group}} \times 100$$

IV. Advantages of the Invention

According to the present invention, there are provided 5-fluorouracil derivatives having cancer metastasis preventing and cancer control effects.

These compounds of the present invention are capable of markedly suppressing the platelet aggregating action induced by arachidonic acid. When these compounds were administered to mice transplanted with cancer cells, the

cancer metastasis was retarded and, in addition, the cancer cells diminished in size. A factor that may have been involved in these phenomena is the platelet aggregating action. In addition, the compounds of the present invention improve the bioavailability of 5-fluorouracil, particularly its absorption by the gut and, hence, they can be used as salient cancer control agents.

Further, the present invention provides a process for producing the above-described 5-fluorouracil derivatives.

It should also be mentioned that no particular abnormalities due to toxicity were found in the above-described test cases on the compounds of the present invention.